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(54) Title: ORAL DOSAGE FORM CONTAINING A PDE 4 INHIBITOR AS AN ACTIVE INGREDIENT AND POLYVINYLPYRROLIDON AS EXCIPIENT

(57) Abstract: Dosage forms for oral administration of a PDE 4 inhibitor whose solubility is slight are described. They contain PVP as binder.

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ORAL DOSAGE FORM CONTAINING A PDE 4 INHIBITOR AS AN ACTIVE INGREDIENT AND  
POLYVINYLPIRROLIDON AS EXCIPIENT

**Technical field**

The present invention relates to the field of pharmaceutical technology and describes a dosage form for oral administration of a PDE 4 inhibitor as active ingredient in tablet or pellet form for treating diseases such as asthma or airway obstructions. The invention additionally relates to processes for producing the dosage form.

**Prior art**

Cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are currently of special interest as a new generation of active ingredients for treating inflammatory disorders, especially inflammations of the airways such as asthma or airway obstructions (such as, for example, COPD = chronic obstructive pulmonary disease). A number of PDE 4 inhibitors is currently undergoing advanced clinical testing.

In WO00/50011 and WO01/32165, which relate to dosage forms with controlled or sustained delivery of a PDE 4 inhibitor, it is pointed out that unwanted CNS side effects may become manifest on delivery of certain PDE 4 inhibitors such as Ariflo® (INN: cilomilast) in higher dosages. WO00/50011 and WO01/32165 see this as being a particular risk with immediate release dosage forms of the active ingredient and therefore propose administering the PDE 4 inhibitor Ariflo® (INN: cilomilast) in dosage forms with controlled or sustained release.

US 5,286,494 proposes a dosage form with controlled or sustained release for the PDE 4 inhibitor Rolipram whose solubility is slight. However, production of dosage forms with controlled or sustained release of slightly soluble active ingredients may be technically complicated, reference being made thereto for example in US 5,286,494.

The solubility of active ingredients of the PDE 4 inhibitor class in water and aqueous systems may, depending on the chemical structure, be low. Thus, the solubility in water found for the PDE 4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast), which is described in WO95/01338, is only 0.53 mg/l at 21°C. The bioavailability of a medicinal substance depends essentially on the release of the medicinal substance from the pharmaceutical form. Faster release and dissolution of the medicinal substance from the formulation means faster absorption thereof. With medicinal substances which are slightly soluble in water, therefore, the bioavailability is frequently limited by the solubility or rate of dissolution. This makes it very difficult to produce suitable dosage forms.

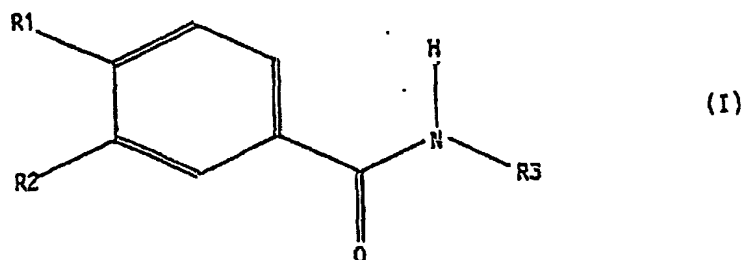
### Description of the invention

It is an object of the present invention to provide a dosage form for oral administration of PDE 4 inhibitors whose solubility is slight, which form can be produced without great technical complexity, which takes account of the low solubility of the PDE 4 inhibitor whose solubility is slight, and which results in rapid, acceptable bioavailability of the PDE 4 inhibitor whose solubility is slight, so as to attain serum levels which are required in order to obtain the desired pharmacological effect quickly without side effects becoming manifest.

It has now been found, surprisingly, that this object can be achieved by a dosage form for oral administration of a PDE 4 inhibitor whose solubility is slight, employing polyvinylpyrrolidone (PVP) as binder for the dosage form. Compared with dosage forms in which no PVP is employed as binder, the dosage form of the invention shows distinctly improved pharmacokinetic properties. Thus, in particular in relation to the bioavailability of the PDE 4 inhibitor whose solubility is slight, a faster absorption and thus faster onset of the pharmacological effect is observed with the dosage forms of the invention compared with dosage forms without PVP. The oral dosage form of the invention is preferably a solid dosage form in tablet or pellet form. It is preferably a solid oral dosage form with immediate release of the active ingredient (immediate release solid oral dosage form).

The invention therefore relates to a dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor whose solubility is slight, comprising the PDE 4 inhibitor whose solubility is slight together with polyvinylpyrrolidone as binder, and one or more other suitable pharmaceutical excipients.

The PDE 4 inhibitor whose solubility is slight is preferably according to the invention a compound from the group of compounds of the formula I



in which either

R1 is 3-7C cycloalkoxy, 3-7C cycloalkylmethoxy or benzyloxy and

R2 is 1-4C alkoxy which is completely or partly substituted by fluorine,

or

R1 is 1-4C alkoxy which is completely or partly substituted by fluorine and

R2 is 3-7C cycloalkylmethoxy or benzyloxy,

and

R3 is phenyl, pyridyl, phenyl substituted by R31, R32 and R33, or pyridyl substituted by R34, R35, R36 and R37, where

R31 is hydroxyl, halogen, cyano, carboxyl, trifluoromethyl, 1-4C alkyl, 1-4C alkoxy, 1-4C alkoxy-carbonyl, 1-4C alkylcarbonyl, 1-4C alkylcarbonyloxy, amino, mono- or di-1-4C alkylamino or 1-4C alkylcarbonylamino,

R32 is hydrogen, hydroxyl, halogen, amino, trifluoromethyl, 1-4C alkyl or 1-4C alkoxy,

R33 is hydrogen, halogen, 1-4C alkyl or 1-4C alkoxy,

R34 is hydroxyl, halogen, cyano, carboxyl, 1-4C alkyl, 1-4C alkoxy, 1-4C alkoxy-carbonyl or amino,

R35 is hydrogen, halogen, amino or 1-4C alkyl,

R36 is hydrogen or halogen and

R37 is hydrogen or halogen,

the salts of these compounds and the N-oxides of the pyridines and the salts thereof.

3-7C Cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C Cycloalkylmethoxy is, for example, cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

Examples which may be mentioned of 1-4C alkoxy which is completely or partly substituted by fluorine are 1,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, perfluoroethoxy and, in particular, 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy and difluoromethoxy radicals.

Halogen for the purposes of the present invention is bromine, chlorine and fluorine.

1-4C Alkyl represents straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C Alkoxy is a radical which, besides the oxygen atom, contains one of the aforementioned 1-4C alkyl radicals. Examples which may be mentioned are the methoxy and ethoxy radicals.

1-4C Alkoxy-carbonyl is a carbonyl group to which one of the aforementioned 1-4C alkoxy radicals is

bonded. Examples which may be mentioned are the methoxycarbonyl ( $\text{CH}_3\text{O}-\text{CO}-$ ) and ethoxycarbonyl ( $\text{CH}_3\text{CH}_2\text{O}-\text{CO}-$ ) radicals.

1-4C Alkylcarbonyl is a carbonyl group to which one of the aforementioned 1-4C alkyl radicals is bonded. An example which may be mentioned is the acetyl radical ( $\text{CH}_3\text{CO}-$ ).

1-4C Alkylcarbonyloxy radicals comprise besides the oxygen atom one of the aforementioned 1-4C alkylcarbonyl radicals. An example which may be mentioned is the acetoxyl radical ( $\text{CH}_3\text{CO}-\text{O}-$ ).

Examples of mono- or di-1-4C alkylamino radicals which may be mentioned are the methylamino, dimethylamino and diethylamino radicals.

An example of a 1-4C alkylcarbonylamino radical which may be mentioned is the acetylamino radical ( $-\text{NH}-\text{CO}-\text{CH}_3$ ).

Examples of phenyl radicals substituted by R31, R32 and R33 which may be mentioned are the radicals 2-acetylphenyl, 2-aminophenyl, 2-bromophenyl, 2-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 4-diethylamino-2-methylphenyl, 4-bromo-2-trifluoromethylphenyl, 2-carboxy-5-chlorophenyl, 3,5-dichloro-2-hydroxyphenyl, 2-bromo-4-carboxy-5-hydroxyphenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl, 2,6-dibromophenyl, 2-cyanophenyl, 4-cyano-2-fluorophenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2-chloro-6-fluorophenyl, 2-hydroxyphenyl, 2-hydroxy-4-methoxyphenyl, 2,4-dihydroxyphenyl, 2-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,6-dimethoxyphenyl, 2-dimethylaminophenyl, 2-methylphenyl, 2-chloro-6-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2,3-dimethylphenyl, 2-methoxycarbonylphenyl, 2-trifluoromethylphenyl, 2,6-dichloro-4-methoxyphenyl, 2,6-dichloro-4-cyanophenyl, 2,6-dichloro-4-aminophenyl, 2,6-dichloro-4-methoxycarbonylphenyl, 4-acetylamino-2,6-dichlorophenyl and 2,6-dichloro-4-ethoxycarbonylphenyl.

Examples of pyridyl radicals substituted by R34, R35, R36 and R37 which may be mentioned are the radicals 3,5-dichloropyrid-4-yl, 2,6-diaminopyrid-3-yl, 4-aminopyrid-3-yl, 3-methylpyrid-2-yl, 4-methylpyrid-2-yl, 5-hydroxypyrid-2-yl, 4-chloropyrid-3-yl, 3-chloropyrid-2-yl, 3-chloropyrid-4-yl, 2-chloropyrid-3-yl, 2,3,5,6-tetrafluoropyrid-4-yl, 3,5-dichloro-2,6-difluoropyrid-4-yl, 3,5-dibromopyrid-2-yl, 3,5-dibromopyrid-4-yl, 3,5-dichloropyrid-4-yl, 2,6-dichloropyrid-3-yl, 3,5-dimethylpyrid-4-yl, 3-chloro-2,5,6-trifluoropyrid-4-yl and 2,3,5-trifluoropyrid-4-yl.

Salts suitable for compounds of the formula I - depending on the substitution - are all acid addition salts but, in particular, all salts with bases. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids and bases normally used in pharmaceutical

technology. Pharmacologically unacceptable salts which, for example, may be the initial products of the process for preparing the compounds of the invention on the industrial scale are converted into pharmacologically acceptable salts by processes known to the skilled worker. Those suitable on the one hand are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid, or 3-hydroxy-2-naphthoic acid, the acids being employed to prepare the salts in the equimolar ratio of amounts, or one differing therefrom - depending on whether the acid is monobasic or polybasic and depending on which salt is desired.

On the other hand, salts with bases are also particularly suitable. Examples of basic salts which may be mentioned are lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, once again the bases being employed to prepare the salts in the equimolar ratio of amounts or one differing therefrom.

Compounds of the formula I to be emphasized are those in which either

R1 is 3-5C cycloalkoxy, 3-5C cycloalkylmethoxy or benzyloxy and

R2 is 1-4C alkoxy which is completely or partly substituted by fluorine,

or

R1 is 1-4C alkoxy which is completely or partly substituted by fluorine and

R2 is 3-5C cycloalkylmethoxy or benzyloxy,

and

R3 is phenyl, pyridyl, phenyl substituted by R31, R32 and R33, or pyridyl substituted by R34, R35, R36 and R37, where

R31 is halogen, cyano, carboxyl, 1-4C alkyl, 1-4C alkoxy or 1-4C alkoxycarbonyl,

R32 is hydrogen, halogen, 1-4C alkyl or 1-4C alkoxy,

R33 is hydrogen, halogen, 1-4C alkyl or 1-4C alkoxy,

R34 is halogen or 1-4C alkyl,

R35 is hydrogen or halogen,

R36 is hydrogen or halogen and

R37 is hydrogen or halogen,

the salts of these compounds, and the N-oxides of the pyridines and salts thereof.

Compounds of the formula I to be particularly emphasized are those in which either

R1 is 3-5C cycloalkoxy, 3-5C cycloalkylmethoxy or benzyloxy and

R2 is 1-4C alkoxy which is completely or partly substituted by fluorine,

or

R1 is 1-4C alkoxy which is completely or partly substituted by fluorine and

R2 is 3-5C cycloalkylmethoxy or benzyloxy and  
R3 is 2-bromophenyl, 2,6-dichloro-4-ethoxycarbonylphenyl, 2,6-dimethoxyphenyl, 4-cyano-2-fluorophenyl, 2,4,6-trifluorophenyl, 2-chloro-6-methylphenyl, 2,6-dimethylphenyl, 2,6-difluorophenyl, 2,6-dichlorophenyl, 3,5-dichloropyrid-4-yl, 3-methylpyrid-2-yl, 2-chloropyrid-3-yl, 3,5-dibromopyrid-2-yl, 2,3,5,6-tetrafluoropyrid-4-yl, 3-chloro-2,5,6-trifluoropyrid-4-yl, 3,5-dichloro-2,6-difluoropyrid-4-yl or 2,6-dichloropyrid-3-yl,  
the salts of these compounds, and the N-oxides of the pyridines and salts thereof.

Preferred compounds of the formula I are those in which

R1 is difluoromethoxy,  
R2 is cyclopropylmethoxy and  
R3 is 2-bromophenyl, 2,6-dichloro-4-ethoxycarbonylphenyl, 2,6-dimethoxyphenyl, 4-cyano-2-fluorophenyl, 2,4,6-trifluorophenyl, 2-chloro-6-methylphenyl, 2,6-dimethylphenyl, 2,6-difluorophenyl, 2,6-dichlorophenyl, 3,5-dichloropyrid-4-yl, 3-methylpyrid-2-yl, 2-chloropyrid-3-yl, 3,5-dibromopyrid-2-yl, 2,3,5,6-tetrafluoropyrid-4-yl, 3-chloro-2,5,6-trifluoropyrid-4-yl, 3,5-dichloro-2,6-difluoropyrid-4-yl or 2,6-dichloropyrid-3-yl,  
the salts of these compounds, and the N-oxides of the pyridines and salts thereof.

A particularly preferred compound of the formula I is the one in which

R1 is difluoromethoxy,  
R2 is cyclopropylmethoxy and  
R3 is 3,5-dichloropyrid-4-yl,  
the salts of these compounds, and the N-oxide of the pyridine and salts thereof.

This compound has the chemical name N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast).

The PDE 4 inhibitor whose solubility is slight is preferably a PDE 4 inhibitor with a solubility in water of less than or equal to 100 milligram/liter, particularly preferably with a solubility in water of less than or equal to 1 milligram/liter, at a temperature of 15 to 25°C, in particular at 21°C. This compound is particularly preferably one of the formula I.

The abovementioned compounds of the formula I and the use of these compounds as phosphodiesterase (PDE) 4 inhibitors are described in the international patent application WO95/01338.

Further suitable pharmaceutical excipients which may be used in the dosage form of the invention are pharmaceutical excipients such as fillers, additional binders, tablet disintegrants or else lubricants and release agents. Other suitable excipients which may be present in the dosage form of the invention are,

for example, *flavoring substances (such as flavors and sweeteners)*, buffer substances, preservatives, coloring substances (such as iron oxid yellow or red) or else emulsifiers. Flavors are usually added in a proportion of from 0.05 to 1% by weight. Other flavoring substances by way of example are acids such as citric acid, sweeteners such as saccharin, aspartame, cyclamate sodium or maltol, which are added according to the desired result.

The polyvinylpyrrolidone (PVP) employed according to the invention is, in particular, a water-soluble PVP with an average molecular weight above 2 000, preferably above 20 000. Examples which may be mentioned are Kollidon 12 PF (molecular weight 2 000-3 000), Kollidon 17 PF (molecular weight 7 000-11 000), Kollidon 25 (molecular weight 28 000-34 000), Kollidon 30 (molecular weight 44 000-54 000), Kollidon 90 F (molecular weight 1 000 000-1 500 000). PVP of higher molecular weight such as, for example, Kollidon 25, Kollidon 30 and Kollidon 90 F may be mentioned as preferred.

It is possible if desired to employ in addition to PVP other binders such as polyvinyl acetate (e.g. Kollidon® VA 64), gelatin, corn starch mucilage, preswollen starches (Starch 1500), hydroxypropyl-methylcellulose (HPMC) or hydroxypropylcellulose (L-HPC).

Fillers suitable according to the invention are fillers such as calcium carbonate (e.g. MagGran® CC or Destab® 95) and sodium carbonate, sugar alcohols such as mannitol (e.g. Perlitol® or Parteck® M), sorbitol (e.g. Karion®), xylitol or maltitol, starches such as corn starch, potato starch and wheat starch, microcrystalline cellulose, saccharides such as glucose, lactose (e.g. lactose monohydrate), levulose, sucrose and dextrose. It is also possible if desired to use mixtures thereof. Corn starch, microcrystalline cellulose and lactose may be mentioned as preferred.

Examples of suitable lubricants and release agents which may be mentioned are sodium stearyl fumarate, magnesium stearate, calcium stearate, stearic acid, talc and colloidal anhydrous silica (Aerosil).

Disintegrants suitable according to the invention are, in particular, insoluble polyvinylpyrrolidone (insoluble PVP, crospovidone), carboxymethylstarch sodium [= sodium starch glycolate], sodium carboxymethylcellulose, alginic acid, and starches able to carry out the function of a disintegrant (e.g. Starch 1500).

The proportion (in percent by weight based on the finished dosage form) of PDE 4 inhibitor in the dosage form of the invention is usually, depending on the nature of the PDE 4 inhibitor, from 0.01 to 50% by weight. The proportion of PDE 4 inhibitor is preferably up to 20% by weight.

The proportion (in percent by weight based on the finished dosage form) of binder (PVP and, where appropriate, other binders) may preferably be according to the invention from 0.5 to 20% by weight. The



proportion of PVP is preferably from 1 to 5% by weight, particularly preferably 2 to 3% by weight.

The proportion (in percent by weight based on the finished dosage form) of filler in the tablet of the invention is advantageously from 40 to 99% by weight. The proportion of filler is preferably from 60 to 97% by weight.

The proportion (in percent by weight based on the finished dosage form) of disintegrant in the rapidly disintegrating tablet can usually be up to 35% by weight. The proportion of disintegrant is preferably from 2 to 20% by weight. The proportion of disintegrant is particularly preferably from 5 to 10% by weight.

The proportion (in percent by weight based on the finished dosage form) of lubricant or release agent in the rapidly disintegrating tablet is usually from 0.1 to 5% by weight. The proportion of lubricant or release agent is preferably from 0.3 to 3% by weight. The proportion of lubricant or release agent is particularly preferably from 0.5 to 2% by weight.

In a preferred embodiment of the invention, the dosage form is a tablet. It is preferred for the tablet, besides the PDE 4 inhibitor whose solubility is slight and PVP, to comprise as further pharmaceutical excipients at least one filler and at least one lubricant or release agent.

The pharmaceutical preparation of the invention can be produced by processes known to the skilled worker for producing tablets and pellets.

In one embodiment of the invention, the pharmaceutical form of the invention is produced by producing a solid solution of the PDE 4 inhibitor whose solubility is slight in the binder PVP as carrier. This can take place for example by the solvent method in which PVP, the PDE 4 inhibitor and, where appropriate, other pharmaceutical excipients are dissolved in a suitable solvent, and the solvent is subsequently removed again by spray drying, normal drying, vacuum drying or freeze-drying. It has been found, surprisingly, that production of the solid solution is also possible by the mixing method in which a PDE 4 inhibitor whose solubility is slight and, where appropriate, other pharmaceutical excipients are vigorously mixed together with PVP.

The invention also relates further to a solid solution of a PDE 4 inhibitor whose solubility is slight in the binder PVP as carrier. A solid solution of the PDE 4 inhibitor in the binder PVP as carrier means according to the invention a solid solution with amorphous structure in which the PDE 4 inhibitor is in the form of a molecular dispersion in the carrier material.

In the event of further processing of a solid solution to tablets or pellets, the solid solution may be processed as active ingredient component together with the filler, binder, disintegrant and lubricant

components by production processes familiar to the skilled worker to give the oral dosage forms of the invention.

The invention therefore also relates to a process for producing a dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor, comprising the steps: (a) production of an active ingredient preparation in the form of a solid solution in PVP of the PDE 4 inhibitor whose solubility is slight, (b) production of a mixture of an active ingredient preparation and pharmaceutical excipients and (c) granulation of the mixture obtained in (b) with an aqueous solution of PVP.

In the case of dosage forms of the invention in the form of tablets, the granules obtained in (c) can, after drying and mixing with lubricants or release agents, be compressed in a tablet press. In the case of dosage forms of the invention in the form of pellets, the wet granules obtained in (c) can be processed by the extruder/spheroidizer process to suitable pellets. Alternatively, dispersions/suspensions of an active ingredient preparation can be applied in the form of a solid solution in PVP of the PDE 4 inhibitor whose solubility is slight in a suitable solvent to pellet-like carriers (e.g. nonpareils or HPMC-containing pellets).

In another preferred embodiment of the invention, the dosage form of the invention is produced by granulating a mixture of active ingredient and pharmaceutical excipients with an aqueous PVP solution, drying the granules and, if desired, admixing other pharmaceutical excipients. Wet preparations obtained after granulation can then be further processed to pellets and can subsequently be packed into capsules. Dried granules can - if desired after admixture of other pharmaceutical excipients - after mixing with a release agent be compressed in a tablet press. The granulation preferably takes place in a fluidized bed granulator under suitable conditions. It is moreover possible if desired for the active ingredient to be admixed to the other pharmaceutical excipients in the form of a trituration with a pharmaceutical excipient (especially a filler). This is particularly preferred when the active ingredient content in the dosage form is less than 5% by weight. Such a trituration can normally be obtained by grinding the active ingredient with a pharmaceutical excipient (especially a filler).

The invention therefore also relates to a process for producing a dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor comprising the steps:

- (a) production of a mixture of active ingredient and pharmaceutical excipients and
- (b) granulation of the mixture obtained in (a) with an aqueous solution of PVP.

The dosage form of the invention is particularly preferably produced by granulation of a mixture of

- (a) PDE 4 inhibitor whose solubility is slight, or a trituration of the PDE 4 inhibitor whose solubility is slight with corn starch,

- (b) corn starch and
- (c) lactose monohydrate

with an aqueous PVP solution, drying of the granules, mixing of the granules with a release agent and compression in a tablet press. The PDE 4 inhibitor whose solubility is slight is in this case particularly preferably roflumilast, the salts thereof, the N-oxide of the pyridine and salts thereof.

Alternatively, the dosage form of the invention is particularly preferably produced by granulation of a mixture of

- (a) PDE 4 inhibitor whose solubility is slight, or a trituration of the PDE 4 inhibitor whose solubility is slight with corn starch,
- (b) corn starch,
- (c) microcrystalline cellulose and
- (d) sodium carboxymethylstarch

with an aqueous PVP solution, drying of the granules, mixing of the granules with a release agent and compression in a tablet press. The PDE 4 inhibitor whose solubility is slight is in this case particularly preferably roflumilast, the salts thereof, the N-oxide of the pyridine and salts thereof.

In a further preferred embodiment of the invention, the dosage form of the invention is produced by granulation of a mixture of pharmaceutical excipients with a suspension of the active ingredient in an aqueous PVP solution, drying of the granules and, if desired, admixture of further pharmaceutical excipients. The preparations obtained in this way can then, after mixing with a release agent, be compressed in a tablet press. The granulation preferably takes place in a fluidized bed granulator under suitable conditions.

The invention therefore also relates to a process for producing a dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor comprising the steps:

- (a) production of a mixture of pharmaceutical excipients and
- (b) granulation of the mixture obtained in (a) with a suspension of the active ingredient in an aqueous solution of PVP.

The dosage form of the invention is particularly preferably produced by granulation of a mixture of corn starch and lactose monohydrate with a suspension of the PDE 4 inhibitor whose solubility is slight in an aqueous solution of PVP, drying of the granules, mixing of the granules with a release agent and compression in a tablet press.

It has surprisingly been found that dosage forms of the invention produced employing physical mixtures or triturations of the PDE 4 inhibitor whose solubility is slight with a filler (e.g. by grinding, vigorous mixing or extrusion) and subsequent granulation with aqueous PVP solutions, or produced employing granulation suspensions of PDE 4 inhibitors in aqueous PVP solutions, have similar advantageous properties in relation to the bioavailability of the PDE 4 inhibitor whose solubility is slight as do dosage forms produced by first producing solid solutions of PVP and PDE 4 inhibitor. This suggests that in the production of the dosage forms of the invention based on physical mixtures or triturations of the PDE 4 inhibitor whose solubility is slight with a filler, which are subsequently granulated with aqueous PVP solutions, or in whose preparation granulation suspensions of PDE 4 inhibitors in aqueous PVP solutions are employed, there are, surprisingly, interactions between PVP and PDE 4 inhibitor whose solubility is slight, like those occurring in the solid solution of PVP and PDE 4 inhibitor. In the production of the dosage forms of the invention it is therefore also possible to dispense with the more technically elaborate variant of production of a solid solution by the solvent method.

#### **Description of the figure**

Figure 1 shows the time course of the average serum concentration of roflumilast after oral administration of 0.5 mg (2 tablets each containing 0.25 mg) of roflumilast from dosage forms of the invention compared with a dosage form containing no PVP.

The production of tablets and preparations of the invention is described by way of example below. The following examples explain the invention in more detail without restricting it.

**Examples****Production of tablets of the invention****Example A****Weight based on a tablet containing 0.1 mg of roflumilast**

1.	Roflumilast (micronized)	0.100 mg
2.	Lactose monohydrate	49.660 mg
3.	Corn starch	13.390 mg
4.	Polyvidone K90	1.300 mg
5.	Magnesium stearate (vegetable)	0.650 mg
	<b>Total</b>	<b>65.100 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.1 mg.

**Example B****Weight based on a tablet containing 0.125 mg of roflumilast**

1.	Roflumilast	0.125 mg
2.	Lactose monohydrate	49.660 mg
3.	Corn starch	13.390 mg
4.	Polyvidone K90	1.300 mg
5.	Magnesium stearate (vegetable)	0.650 mg
	<b>Total</b>	<b>65.125 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.125 mg.

**Example C****Weight based on a tablet containing 0.25 mg of roflumilast**

1.	Roflumilast	0.250 mg
2.	Microcrystalline cellulose	33.900 mg
3.	Corn starch	2.500 mg
4.	Polyvidone K90	2.250 mg
5.	Sodium carboxymethylstarch (type A)	20.000 mg
6.	Magnesium stearate (vegetable)	0.600 mg
	<b>Total</b>	<b>59.500 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2), (5) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (6) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 59.5 mg.

**Example D****Weight based on a tablet containing 0.25 mg of roflumilast**

1.	Roflumilast	0.250 mg
2.	Lactose monohydrate	49.660 mg
3.	Corn starch	13.390 mg
4.	Polyvidone K90	1.300 mg
5.	Magnesium stearate (vegetable)	0.650 mg
	<b>Total</b>	<b>65.250 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.25 mg.

**Example E****Weight based on a tablet containing 0.5 mg of roflumilast**

1.	Roflumilast	0.500 mg
2.	Lactose monohydrate	49.660 mg
3.	Corn starch	13.390 mg
4.	Polyvidone K90	1.300 mg
5.	Magnesium stearate (vegetable)	0.650 mg
	<b>Total</b>	<b>65.500 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.500 mg.

**Example F****Weight based on a tablet containing 0.5 mg of roflumilast**

1.	Roflumilast	0.500 mg
2.	Lactose monohydrate	99.320 mg
3.	Corn starch	26.780 mg
4.	Polyvidone K90	2.600 mg
5.	Magnesium stearate (vegetable)	1.300 mg
	<b>Total</b>	<b>130.500 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 130.5 mg.

**Example G**

**Weight based on a tablet containing 2.5 mg of roflumilast**

1.	Roflumilast	2.500 mg
2.	Microcrystalline cellulose	33.900 mg
3.	Corn starch	2.500 mg
4.	Polyvidone K90	2.250 mg
5.	Sodium carboxymethylstarch (type A)	20.000 mg
6.	Magnesium stearate (vegetable)	0.600 mg
	<b>Total</b>	<b>61.750 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2), (5) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (6) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 61.75 mg.

**Example H**

**Production of tablets containing 0.1 mg of roflumilast as active ingredient (weight for a batch of 70 000 tablets)**

1.	Roflumilast (micronized)	7.000 g
2.	Lactose monohydrate	3476.200 g
3.	Corn starch	937.300 g
4.	Polyvidone K90	91.000 g
5.	Magnesium stearate (vegetable)	45.500 g
	<b>Total</b>	<b>4557.000 g</b>

**Production:** (1) is mixed with 70 g of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on. (Spraying pressure: 3 bar; product temperature: 28-33°C; air flow rate in the first third of the spraying process: 100 m<sup>3</sup>/h; air flow rate subsequently during the spraying process: 150 m<sup>3</sup>/h; inlet air temperature: 40-70°C; spraying rate: 30-40 g/min). After spraying is complete, drying is carried out until the product temperature reaches 34°C. The granules are passed through a stainless steel sieve with a mesh width of 0.8 mm, and the relative surface moisture is measured and adjusted to a value in the range 20-50%.



(5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.1 mg.

#### **Example I**

**Production of tablets containing 0.25 mg of roflumilast as active ingredient (weight for a batch of 70 000 tablets)**

1.	Roflumilast (micronized)	35.000 g
2.	Lactose monohydrate	3476.200 g
3.	Corn starch	937.300 g
4.	Polyvidone K90	91.000 g
5.	Magnesium stearate (vegetable)	45.500 g
	<b>Total</b>	<b>4585.000 g</b>

**Production:** 19.25 g of (1) are mixed with 192.5 g of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on. (Spraying pressure: 3 bar; product temperature: 28-33°C; air flow rate in the first third of the spraying process: 100 m<sup>3</sup>/h; air flow rate subsequently during the spraying process: 150 m<sup>3</sup>/h; inlet air temperature: 40-70°C; spraying rate: 30-40 g/min). After spraying is complete, drying is carried out until the product temperature reaches 34°C. The granules are passed through a stainless steel sieve with a mesh width of 0.8 mm, and the relative surface moisture is measured and adjusted to a value in the range 20-50%. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.5 mg.

#### **Example J**

**Production of tablets containing 0.1 mg of roflumilast as active ingredient (weight for a batch of 70 000 tablets)**

1.	Roflumilast (micronized)	7.000 g
2.	Lactose monohydrate	3476.200 g
3.	Corn starch	937.300 g
4.	Polyvidone K90	91.000 g
5.	Magnesium stearate (vegetable)	45.500 g
	<b>Total</b>	<b>4557.000 g</b>

**Production:** (1) is homogeneously suspended in a granulation solution of (4) in purified water. (2) and (3) are put into the product container of a suitable fluidized bed granulation system and granulated with the granulation suspension described above, and then dried. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.1 mg.

#### **Example K**

**Production of tablets containing 0.25 mg of roflumilast as active ingredient (weight for a batch of 70 000 tablets)**

1.	Roflumilast (micronized)	35.000 g
2.	Lactose monohydrate	3476.200 g
3.	Corn starch	937.300 g
4.	Polyvidone K90	91.000 g
5.	Magnesium stearate (vegetable)	45.500 g
	<b>Total</b>	<b>4585.000 g</b>

**Production:** (1) is homogeneously suspended in a granulation solution of (4) in purified water. (2) and (3) are put into the product container of a suitable fluidized bed granulation system and granulated with the granulation suspension described above, and then dried. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.25 mg.

#### **Example L**

**Weight based on a tablet containing 0.25 mg of roflumilast**

1.	Roflumilast	0.250 mg
2.	Lactose monohydrate	49.660 mg
3.	Potato starch	10.000 mg
4.	Corn starch	3.590 mg
5.	PVP 25	1.500 mg
6.	Magnesium stearate (vegetable)	0.650 mg
	<b>Total</b>	<b>65.650 mg</b>

**Production:** A dispersion is produced from (4) and water, and (1) is homogeneously suspended therein. (5) is dissolved in water and added to the dispersion. (2) and (3) are granulated in a suitable fluidized

bed granulation system with the dispersion under suitable conditions. (6) is added to this mixture, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.650 mg.

#### **Example M**

##### **Weight based on a tablet containing 0.25 mg of roflumilast**

1.	Roflumilast	0.250 mg
2.	Lactose monohydrate	49.660 mg
3.	Corn starch	13.390 mg
4.	Polyvidone K90	1.300 mg
5.	Gelatin	1.300 mg
6.	Magnesium stearate (vegetable)	0.650 mg
	<b>Total</b>	<b>66.550 mg</b>

**Production:** (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) and (5) in purified water is sprayed on and dried under suitable conditions. (6) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 66.55 mg.

#### **Example M1**

Formulation for pediatric use

##### **Weight based on a tablet containing 0.125 mg of roflumilast**

1.	Roflumilast	0.125 mg
2.	Lactose monohydrate	49.660 mg
3.	Corn starch	13.390 mg
4.	Polyvidone K90	1.300 mg
5.	Mannit	32.238 mg
6.	Flavor (Tutti Frutti)	0.329 mg
7.	PVP (insoluble)	12.895 mg
5.	Magnesium stearate (vegetable)	1.649 mg
	<b>Total</b>	<b>111.586 mg</b>

The formulation is produced according to a process disclosed above.

**Physical investigations and comparative tests with dosage forms in which no PVP was used as binder**

**Example N**

The disintegration time and the release of active ingredient were determined for a dosage form corresponding to example D.

Disintegration time: the disintegration time was determined using a disintegration tester by the method described in the European Pharmacopoeia.

Result: 7.08 minutes.

Release of active ingredient: the release of active ingredient was determined as described in the US Pharmacopeia (USP XXV; apparatus 2).

Result: 78% of the active ingredient are released after 15 minutes, and quantitative release is observed after 60 minutes.

**Example O**

Production of a dosage form containing roflumilast in which no PVP is used:

**Weight based on a tablet containing 0.25 mg of roflumilast**

1.	Roflumilast	0.250 mg
2.	Lactose monohydrate	70.300 mg
3.	Potato starch	19.475 mg
4.	Corn starch	3.563 mg
5.	Sodium carboxymethylstarch (Type A)	1.900 mg
6.	Magnesium stearate (vegetable)	0.950 mg
	<b>Total</b>	<b>96.438 mg</b>

Production: A dispersion is produced from (4) and water, and (1) is homogeneously suspended therein. (2) and (3) are granulated in a suitable fluidized bed granulation system with the dispersion under suitable conditions. (5) is added to the dry granules, and a homogeneous mixture is produced. (5) is added to this mixture, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 96.438 mg.

**Comparative study**

Design: 24 subjects, 3-period changeover, randomized; dose in each case 0.5 mg (2 tablets each containing 0.25 mg of roflumilast). The serum concentration of roflumilast after oral administration of 0.5 mg (2 tablets each containing 0.25 mg) of roflumilast was investigated for the following dosage forms:

**With PVP as binder:**

Tablet corresponding to example D, referred to as "treatment A" hereinafter.

Tablet corresponding to example K, referred to as "treatment B" hereinafter.

**Without PVP as binder:**

Tablet corresponding to example O, referred to as "treatment C" hereinafter.

The results are depicted in figure 1. Higher serum levels were observed considerably more quickly after oral administration for dosage forms with PVP as binder compared with dosage forms without PVP. The rate of absorption is thus distinctly increased for the dosage forms of the invention.

**Industrial applicability**

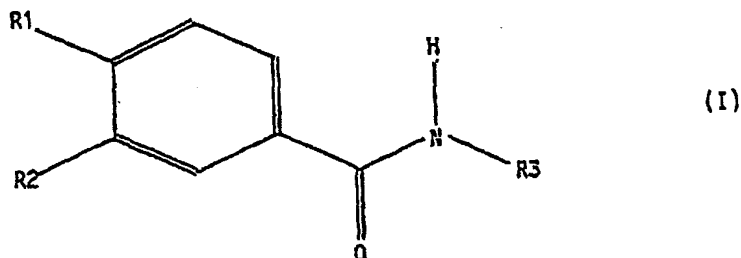
The dosage forms of the invention can be employed for the treatment and prevention of all diseases regarded as treatable or preventable through the use of PDE 4 inhibitors. Selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are suitable on the one hand as bronchial therapeutic agents (for the treatment of airway obstructions owing to their dilating effect but also owing to their effect increasing the respiratory rate and respiratory drive) and for eliminating erectile dysfunction owing to the vasodilating effect, but on the other hand especially for the treatment of disorders, especially of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the central nervous system, of the intestine, of the eyes and of the joints, which are promoted by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. The pharmaceutical preparations of the invention can therefore be used in human and veterinary medicine for example for the treatment and prophylaxis of the following diseases: acute and chronic (especially inflammatory and allergen-induced) airway disorders of various etiologies (bronchitis, allergic bronchitis, bronchial asthma, COPD); dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrheic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders based on excessive release of TNF and leukotrienes, e.g. disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states), disorders of the immune system (AIDS, multiple sclerosis), types of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)] and generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders based on allergic and/or chronic abnormal immunological reactions in the region of the upper airways (pharyngeal space, nose) and adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and nasal polyps; but also cardiac disorders which can be treated by PDE inhibitors, such as, for example, heart failure, or disorders which can be treated owing to the tissue-relaxant effect of PDE inhibitors, such as, for example, erectile dysfunction or colic of the kidneys and ureters connected with kidney stones; or else disorders of the CNS such as, for example, depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, suffering from one of the abovementioned diseases. The method is characterized by administration of a therapeutically effective and pharmacologically suitable amount of a PDE 4 inhibitor to the mammalian patient, the PDE 4 inhibitor being present in a dosage form of the invention. The disease is preferably asthma or airway obstructions, especially COPD (= chronic obstructive pulmonary disease).

The dosage forms of the invention comprise the PDE 4 inhibitor in the dose customary for the treatment of the particular disease. The dosage of the active ingredient is of the order of magnitude customary for PDE inhibitors, it being possible to administer the daily dose in one or more dosage units. The normal dose on systemic therapy (oral) is between 0.001 mg and 3 mg per kilogram and day. Dosage forms preferred according to the invention contain from 0.01 mg to 5 mg of roflumilast, preferably from 0.05 mg to 2.5 mg, particularly preferably 0.1 mg to 0.5 mg of roflumilast per dosage unit. Examples of pharmaceutical preparations of the invention contain 0.1 mg, 0.125 mg, 0.25 mg and 0.5 mg of roflumilast per dosage unit. Normally, one or more than one dosage unit of the invention is administered once a day. If desired, it is also possible for one or more dosage units of the invention to be administered more than once a day.

**Claims**

1. A dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor whose solubility is slight, comprising the PDE 4 inhibitor whose solubility is slight together with polyvinylpyrrolidone as binder, and one or more other suitable pharmaceutical excipients.
2. The dosage form as claimed in claim 1, where the pharmaceutical excipients are excipients from the group of fillers, binders and lubricants or release agents.
3. The dosage form as claimed in claim 1, which is a solid oral dosage form with immediate release of active ingredient (immediate release solid oral dosage form).
4. The dosage form as claimed in claim 1, which is a tablet.
5. The dosage form as claimed in claim 1, where the PDE 4 inhibitor whose solubility is slight is a compound having a solubility in water of less than or equal to 100 milligram/liter at a temperature of from 15 to 25°C.
6. The dosage form as claimed in claim 1, where the PDE 4 inhibitor is a compound selected from the group of compounds of the formula I



in which either

R1 is 3-7C cycloalkoxy, 3-7C cycloalkylmethoxy or benzyloxy and

R2 is 1-4C alkoxy which is completely or partly substituted by fluorine,

or

R1 is 1-4C alkoxy which is completely or partly substituted by fluorine and

R2 is 3-7C cycloalkylmethoxy or benzyloxy,

and

R3 is phenyl, pyridyl, phenyl substituted by R31, R32 and R33, or pyridyl substituted by

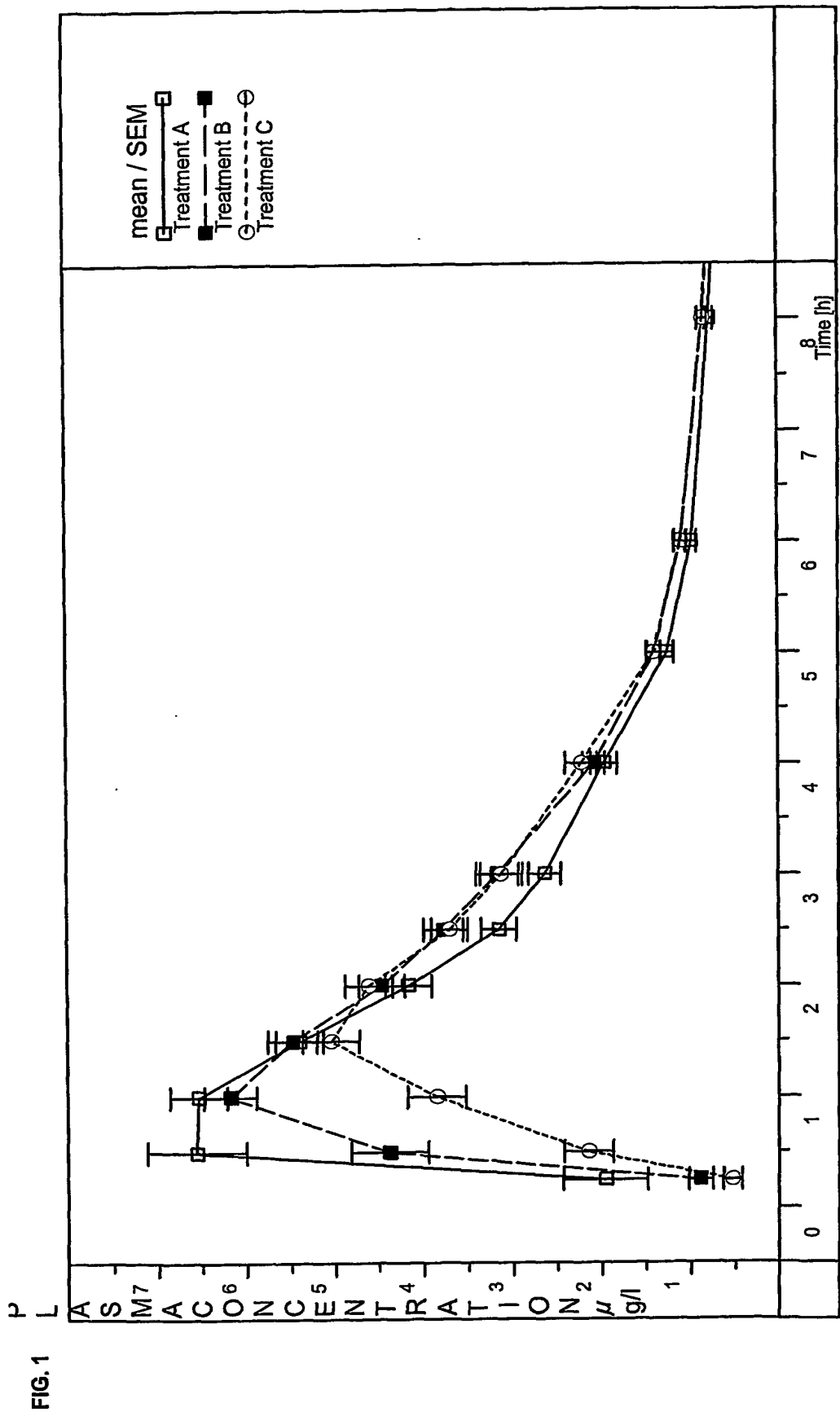


R34, R35, R36 and R37, where

- R31 is hydroxyl, halogen, cyano, carboxyl, trifluoromethyl, 1-4C alkyl, 1-4C alkoxy, 1-4C alkoxycarbonyl, 1-4C alkylcarbonyl, 1-4C alkylcarbonyloxy, amino, mono- or di-1-4C alkylamino or 1-4C alkylcarbonylamino,
- R32 is hydrogen, hydroxyl, halogen, amino, trifluoromethyl, 1-4C alkyl or 1-4C alkoxy,
- R33 is hydrogen, halogen, 1-4C alkyl or 1-4C alkoxy,
- R34 is hydroxyl, halogen, cyano, carboxyl, 1-4C alkyl, 1-4C alkoxy, 1-4C alkoxycarbonyl or amino,
- R35 is hydrogen, halogen, amino or 1-4C alkyl,
- R36 is hydrogen or halogen and
- R37 is hydrogen or halogen,

the salts of these compounds and the N-oxides of the pyridines and the salts thereof.

7. The dosage form as claimed in claim 6, which comprises a compound of the formula I in which  
R1 is difluoromethoxy,  
R2 is cyclopropylmethoxy and  
R3 3,5-dichloropyrid-4-yl,  
the salts of this compound, and the N-oxide of the pyridine and salts thereof.
8. A process for producing a dosage form as claimed in claim 1, comprising the steps:  
(a) production of a mixture of PDE 4 inhibitor and pharmaceutical excipients and (b) granulation of the mixture obtained in (a) with an aqueous solution of PVP.
9. A process for producing a dosage form as claimed in claim 1, comprising the steps:  
(a) production of a mixture of pharmaceutical excipients and  
(b) granulation of the mixture obtained in (a) with a suspension of the active ingredient in an aqueous solution of PVP.
10. A process for producing a dosage form as claimed in claim 1, comprising the production of a solid solution of PVP and PDE 4 inhibitor whose solubility is slight.
11. A method for the treatment or prophylaxis of a disease regarded as treatable or preventable by PDE 4 inhibitors, wherein a dosage form as claimed in claim 1 is administered.



# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/01650

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K45/06 A61K9/20 A61K31/166 A61K31/44 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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X	EP 1 120 120 A (EISAI CO LTD) 1 August 2001 (2001-08-01) * p.2, 1.12-13; p.5, 1.35; claim 1-17 *	1-10
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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/01650

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